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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/819,248	03/27/2001	Scott A. Waldman	08321-0162 US	2089

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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/819,248	WALDMAN ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) _____ is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgment is made of applicant election of the species of CdX2 without traverse.

Claims 1-15 are pending and examined on the merits.

Acknowledgement is made of applicants priority claim to provisional application 60/192,229. After review of the '229 application it is concluded that said application lacks support for the instant method claims. the instant methods are drawn to a method for identifying molecular markers useful for detecting metastatic tumor cells, said method comprising the downregulation of a transcription factor associated with terminally differentiated tissue in a population of origin cells, and the comparison of the resulting expression profile is said origin cells with the expression profile of control cells, wherein a "candidate marker" which is expressed in the population of origin cells having undergone downregulation of said transcription factor, but not present in said control cells is useful is "useful" as a molecular marker for the determination of metastatic cancer.

Claim 13 of the instant application lists CdX2 as a specific transcription factor of claim 1. Thus a specific embodiment of the instant method claim requires the downregulation of CdX2 in a population of cells, and the measurement of the resulting expression profile, wherein proteins which are overexpressed as a result of this downregulation are classified as useful markers for metastatic cancer. the '29 application describes methods wherein the detection of CdX2 indicates specifically primary and metastasized esophageal and stomach cancer. the '229 application states that metastatic esophageal and metastatic stomach cancer may be indicated by the detection of CdX2 in samples of non-esophageal and non-stomach origin (page 2, lines 20-28). Thus, the '229 application lacks adequate written description of a method reliant on the detection of markers other than CdX2 produced when CdX2 expression is downregulated. Accordingly, the instant application is given the priority date of filing March 27, 2001.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 6-11, and 13-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mack (WO 98/30722) in view of Mallo et al (International Journal of Cancer, 1997, Vol. 74, pp. 35-44) and Mallo et al (Journal of Biological Chemistry, 1998, Vol. 273, pp. 14030-140360).

Mack teaches a methods comprising gene expression monitoring for determining the function of a gene and the use of specific mutations of upstream genes or antisense oligonucleotides can be used to block the expression of specific genes in order to assess their impact on the expression of downstream genes (page 2, lines 13-16 and lines 30-32 and page 2, line 34 to page 3, line 2). Mack teaches that these methods have a wide variety of application, such as in the field of diagnostics (page 3, line 11-12) Mack specifically teaches methods in which the expression of a large number of genes is monitored in biological samples with the target gene expression to produce a control expression profile (page 4, lines 8-10). Mack teaches that the expression of the target gene is then suppressed to produce a target expression profile, and that by comparing the expression profile with the target expression profile, one can identify potential regulated down-stream genes from affected genes (page 4, lines 10-12). Mack teaches as a generic example an upstream gene which is a transcription factor which controls the expression of a second gene (page 13, lines 15-19 and page 41, lines 19-28). Mack teaches that both negatively and positively regulated downstream genes can be simultaneously monitored (page 14, lines 24-28). Mack teaches that the regulatory function of a particular gene can be

identified by monitoring a large number of genes and that in a particular preferred embodiment , the expression of a gene of interest is suppressed by applying antisense oligonucleotide and the resulting expression pattern is then monitored (page 14, lines 29-33). Mack teaches that the monitoring of gene expression profiles can be carried out by Northern blotting and hybridization, nuclease protection, differential display, and SAGE (page 37, lines 27-35), thus fulfilling the specific embodiments of claim 4 . Mack et al do not specifically teach the down-regulation of CdX2 by means of antisense, or down-regulating the activity of CdX2 by means of a mutation, or the correlation between genes expressed in down-regulated origin cells and useful molecular markers for metastasis obtained thereby.

Mallo (1997)et al teach that the transformation of a cell and the acquisition of the invasive and metastatic phenotypes result form the activation of the complex cellular processes rather than the effect of a single gene product. Mallo et al teach that it is likely that the coordination of the multiple genes involved in malignancy is under the control of a few master genes and that these master genes probably include transcription factors that control genetic programs allowing for tumor invasion and metastasis (page 37, second column, lines 1-8 under the heading "Discussion"). Mallo et al teach that homeobox genes are a family of transcription factors whose expression has been found to be altered in a variety of malignant tissues (page 37, second column, lines 10-18 under the heading "Discussion"). Mallo et al teach that malignant transformation can be mediated through selective transcription repression of homeobox genes and concludes that homeobox genes play a key role in development, differentiation and cancer (page 37, second column, lines 19-24 under the heading "Discussion"). Mallo et al teach that decreased CdX2 expression is associated with progression to more advanced stages of colorectal tumorigenesis ((page 39, first column, lines 4-5). Mallo et al teach that an analysis involving a larger number of cases is needed to characterize the relation between the patter of expression of CdX genes and colon-cancer progression (page 39-43, bridging sentence) and that the down-regulated transcriptional factors, CdX1 and CdX2 homeobox genes are potential tumor suppressor genes (page 43, second column, lines 3-4). Mallo et al teach that in the analysis of cell lines derived from colorectal carcinoma indicated that only the CdX2 transcript and not the CdX1 transcript was present in the SW480 cell line and neither of the CdX1 nor CdX2 transcripts were present in the Ht29 cell lines.

Mallo et al (1998) teach that migratory ability is necessary for tumor invasivity and metastasis (page 14035, second column, lines 18-20). Mallo et al teach that restoration of CdX2 expression in HT29 cells significantly inhibited PMA-stimulated migration of said cells (page 14035, second column, lines 24-28). Mallo et al concludes that it is likely that loss of CdX2 expression from normal colonic cells would significantly increase their migration potential (page 14035, second column, lines 20-22).

It would have been prima facie obvious to one of skill in the art at the time the invention was made to investigate the expression of gene products associated with the negative regulatory functions of CdX2 by comparing the expression profile of the CdX2 transfected HT29 cell line with the expression profile of the untransfected HT29 cell line in the method taught by Mack. One of skill in the art would be motivated to do so by the teachings of Mallo et al (1997) regarding the correlation progression to more advanced stages of cancer and decreased CdX2 expression; and the teaching of Mallo et al (1998) on the loss of expression of CdX2 and the increase in migratory potential of tumor cells. One of skill in the art would recognize that the comparison of gene expression profiles from the wild-type HT29 cells which do not express CdX2 and the transfected HT29 cells which express CdX2 is analogous to the method taught by Mack comprising the suppression of target genes by antisense oligonucleotides and the study of negatively regulated down stream genes by the suppression of said target gene. It would be further obvious to use origin and destination tissues, as well as CdX2-null intestinal polyps because Mallo et al (1997) teaches that in tissue samples from human colorectal carcinomas expression of CdX2 was either reduced or absent in 10 out of 12 samples analyzed (abstract, lines 24-27)., thus fulfilling the specific embodiments of claims 3, 6-8, 10 regarding destination and origin tissues. further, the specific embodiment of claim 15 would be fulfilled by the disclosure of Mallo et al (1997) that the CdX2 gene is a homeobox transcription factor. Claim 15 appears to be defining the a "product" (i.e. the transcription factor) by a process. However, the disclosure of the CdX2 gene as encoding a transcription factor metes the limitation said product by process claim because the CdX2 transcription factor disclosed in the prior art has the same properties as the transcription factor obtained by the process of claim 15.

It would also be obvious to isolate the molecular marker determined in step d of claim 1. One of skill in the art would be motivated to do so in order to prepare a nucleic acid probe or an

antibody which would bind to said marker. One of skill in the art would know that said probe or antibody can be used to identify advanced stage colorectal carcinomas and metastatic colorectal carcinomas because of the teaching rendered obvious by the combination of Mallo et al (1997) and Mallo et al (1998).

Claims 1-11, and 13-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mack (WO 98/30722) and Mallo et al (International Journal of Cancer, 1997, Vol. 74, pp. 35-44) and Mallo et al (Journal of Biological Chemistry, 1998, Vol. 273, pp. 14030-140360). as applied to claims 1-4, 6-11, and 13-15 above, and further in view of Keesee et al (US 6,218,131).

Claim 5 contains the specific embodiment of 2-D gel electrophoresis.

Mallo et al (1998) teach that the downregulation of CdX2 genes in colorectal cancer was verified by immunohistochemistry (page 14030, second column, lines 5-9). thus, one of skill in the art would conclude that the level of gene expression of the CdX2 gene is correlated to the level of protein translation of CdX2. Mallo et al does not specifically teach the detection of tumor marker protein by 2-D gel electrophoresis.

Keesee et al (US 6,218,131) teach the detection of breast cancer marker protein by 2-D gel electrophoresis (column 5, lines 42-45).

It would have been prima facie obvious to one of skill in the art that the tumor markers identified by the downregulation of CdX2 could be measured by 2-D gel electrophoresis. One of skill in the art would have been motivated to do so by the teachings of Keessee et al on the detection of breast cancer marker proteins by 2D gels.

Claims 1-4, 6-11, and 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mack (WO 98/30722) and Mallo et al (International Journal of Cancer, 1997, Vol. 74, pp. 35-44) and Mallo et al (Journal of Biological Chemistry, 1998, Vol. 273, pp. 14030-140360). as applied to claims 1-4, 6-11, and 13-15 above, and further in view of the abstract of Wolmark et al (Cancer, 1983, Vol. 51, pp. 1315-1322) or the abstract of Denis et al, European Journal of Cancer, 1996, Vol. 32A, suppl. 1, page S27).

Claim 12 embodies the method of claim 1 wherein the destination tissue or fluid is selected from lymph node, blood, CSF and bone marrow.

The abstract of Wolmark et al teaches taught colorectal cancer metastasizes to the lymph nodes. The abstract of Denis et al teaches that colorectal carcinoma metastases can be detected in the blood.

It would have been prima facie obvious to one of skill in the art at the time the invention was made to use blood or lymph node as the destination tissue because it is taught in the art that colorectal cancer metastasizes to said tissues and fluids.

Claims 1-11, and 13-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lazaridis (US 2003/0023385 A1, priority to 60/180,282, filed Feb 4, 2000) in view of Mallo et al (International Journal of Cancer, 1997, Vol. 74, pp. 35-44) and Mallo et al (Journal of Biological Chemistry, 1998, Vol. 273, pp. 14030-140360).

Lazaridis teaches that the capacity to predict metastatic potential through analysis of gene expression patterns is desirable [0002]. Lazaridis teaches a method wherein the patterns of gene expression that portend metastasis may be deciphered from tumor specimens. Lazaridis teaches that a successful deciphering method identified in a genomic library a gene or set of genes linked to the metastatic properties of cancer, and is also applicable to the classification of patients with tumor samples having high versus low metastatic potential [0011]. Lazaridis teaches that the expression of transcription factors depends on the quantities of transcription factor complexes an other molecules that associated with said transcription factors before transcription can occur [0012]. Lazaridis teaches a method to identify genes linked to a disease via analysis of cell or tissue samples, and to identify disease status in individuals suspected of having the disease [0014]. Lazaridis teaches that a preferred embodiment of the method entails the determination of correlation between protein expression and RNA expression in deciphering patterns portending to cancer metastasis[0015 and 0018], and that representative cancers include colon carcinoma[0015]. Lazaridis teaches the human metastatic variant cell lines of KM12 C, KM12 SM, KM12I4A, SW480 and SW620 and teaches the identification of metastatic genes common to said cell lines [0019]. Lazaridis teaches the monitoring of gene expression by 2-D gel analysis of proteins [0075 and 0076], thus fulfilling the specific embodiment of claim 5 drawn to 2-D gel electrophoresis. Lazaridis does not specifically teach the down-regulation of CdX2 by means of antisense, or down-regulating the activity of CdX2 by means of a mutation, or the

correlation between genes expressed in down-regulated origin cells and useful molecular markers for metastasis obtained thereby.

Mallo (1997)et al teach that the transformation of a cell and the acquisition of the invasive and metastatic phenotypes result form the activation of the complex cellular processes rather than the effect of a single gene product. Mallo et al teach that it is likely that the coordination of the multiple genes involved in malignancy is under the control of a few master genes and that these master genes probably include transcription factors that control genetic programs allowing for tumor invasion and metastasis (page 37, second column, lines 1-8 under the heading "Discussion"). Mallo et al teach that homeobox genes are a family of transcription factors whose expression has been found to be altered in a variety of malignant tissues (page 37, second column, lines 10-18 under the heading "Discussion"). Mallo et al teach that malignant transformation can be mediated through selective transcription repression of homeobox genes and concludes that homeobox genes play a key role in development, differentiation and cancer (page 37, second column, lines 19-24 under the heading "Discussion"). Mallo et al teach that decreased CdX2 expression is associated with progression to more advanced stages of colorectal tumorigenesis ((page 39, first column, lines 4-5). Mallo et al teach that an analysis involving a larger number of cases is needed to characterize the relation between the patter of expression of CdX genes and colon-cancer progression (page 39-43, bridging sentence) and that the down-regulated transcriptional factors, CdX1 and CdX2 homeobox genes are potential tumor suppressor genes (page 43, second column, lines 3-4). Mallo et al teach that in the analysis of cell lines derived from colorectal carcinoma indicated that only the CdX2 transcript and not the CdX1 transcript was present in the SW480 cell line and neither of the CdX1 nor CdX2 transcripts were present in the Ht29 cell lines.

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It would have been prima facie obvious to one of skill in the art at the time the invention was made to investigate the expression of gene products associated with the negative regulatory functions of CdX2 by comparing the expression profile of the CdX2 transfected HT29 cell line with the expression profile of the untransfected HT29 cell line in the method taught by Lazaridis. One of skill in the art would be motivated to do so by the teachings of Mallo et al (1997) regarding the correlation progression to more advanced stages of cancer and decreased CdX2 expression; and the teaching of Mallo et al (1998) on the loss of expression of CdX2 and the increase in migratory potential of tumor cells. One of skill in the art would recognize that the comparison of gene expression profiles from the wild-type HT29 cells which do not express CdX2 and the transfected HT29 cells which express CdX2 is analogous to the method taught by Mack comprising the suppression of target genes by antisense oligonucleotides and the study of negatively regulated down stream genes by the suppression of said target gene. It would be further obvious to use origin and destination tissues, as well as CdX2-null intestinal polyps because Mallo et al (1997) teaches that in tissue samples from human colorectal carcinomas expression of CdX2 was either reduced or absent in 10 out of 12 samples analyzed (abstract, lines 24-27)., thus fulfilling the specific embodiments of claims 3, 6-8, 10 regarding destination and origin tissues. further, the specific embodiment of claim 15 would be fulfilled by the disclosure of Mallo et al (1997) that the CdX2 gene is a homeobox transcription factor. Claim 15 appears to be defining the a "product" (i.e. the transcription factor) by a process. However, the disclosure of the CdX2 gene as encoding a transcription factor metes the limitation said product by process claim because the CdX2 transcription factor disclosed in the prior art has the same properties as the transcription factor obtained by the process of claim 15.

It would also be obvious to isolate the molecular marker determined in step d of claim 1. One of skill in the art would be motivated to do so in order to prepare a nucleic acid probe or an antibody which would bind to said marker. One of skill in the art would know that said probe or antibody can be used to identify advanced stage colorectal carcinomas and metastatic colorectal carcinomas because of the teaching rendered obvious by the combination of Mallo et al (1997) and Mallo et al (1998).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on (571)272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
Art Unit 1642
03/22/04